REMARKS

Claims 2, 4, and 25-28 have been cancelled. Claims 1, 3, 19, and 20 have been amended. New claims 29-50 are added. Claims 1, 3, 5-24, and 29-50 are now pending in this application. Support for the amendments is found in the existing claims and the specification as discussed below. Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

Claim amendments

Claims 1 and 3 have been amended to clarify the claimed subject matter. Support for the amendment is found, for example in paragraph [0008], l.5-7, paragraph [0008], l.10-14 and paragraph [0024], l.1-6 of the '397 application as published. That said dendritic cells may also be an intermediate between dendritic cells and monocytes is covered in new claims 31 and 39. Said claims refer to the dendritic cells as proliferating dendritic cells or a dendritic cell at a more immature stage.

New claims 33, 34, 35, 41, 42, 43 and 47-50 find support, for example, in paragraph [0081], l.1-4 of the '397 application as published.

Claims 19 and 20 have been amended for clarity reasons, changing "derived" to "purified". Support for said amendment may be found in for instance paragraph [0081], l.1-4 and l.7-8 of the '397 application as published.

New claims 31 and 39 find support, for example, in paragraph [0184], l.9-10 of the '397 application as published.

New claims 29 and 30 find support, for example, in paragraph [0016], l.1-5 and [0019], l.2-4 of the '397 application as published. Said paragraphs indicate that the anti-tumor response elicited in a subject, as proposed in the present invention, may be transposable to human patients. The invention further suggests that preferably autologous DCs (human) and tumor cells derived

from the patient (human) are used. This is discussed throughout the present specification (e.g. examples 7 and 8).

New claims 32 and 40 find support, for example, in paragraph [0084], l.1-4 of the '397 application as published. This paragraph teaches that DCs differentiated from human blood may be cultured for at least 7 days. A skilled person understands that said cells are proliferating. Consequently, proliferating DCs or DCs at a more immature stage may also be made or isolated from human blood, bone marrow or other tissues.

New claims 38 and 46 find support, for example, in paragraph [0081], l.9-13 of the '397 application as published.

That dendritic cells may be of myeloid or lymphoid origin is taught in paragraph [0024] of the '397 application as published. This paragraph further mentions that DLCs may be an intermediate between dendritic cells and monocytes. It is known that monocytes may give rise to DCs of both myeloid and lymphoid origin. Therefore, a skilled person may derive from said paragraph that said intermediate may also be referred to as an intermediate of myeloid or lymphoid origin. This provides support for **new claims 36, 37, 44 and 45.**

Claims 25 to 28 have been cancelled.

Declaration/Oath

The Examiner objects to the **Declaration** because of uninitialed changes in the residence address of Inventor Lespagnard. Applicants submit a corrected Declaration and Power of Attorney herewith. Applicants request that this objection be withdrawn.

Priority of US 09/802,397.

The present application was filed on March 9, 2001, published on August 9, 2001 and claims the priority dates of March 27, 1998 ('502), February 18, 1998 ('405), March 29, 1996 ('507) and March 31, 1995 ('480).

Amended claims 1 and 3

The Examiner states that due to the broad interpretation of the term "dendritic cells", the instant application is granted the benefit of priority of the '507 application (March 29, 1996), with exception of previous claims 34, 39 and 41 (see below).

With this amendment, a new definition for the dendritic cells is introduced based on the disclosure of paragraph [0008], l.5-7, paragraph [0008], l.10-14 and paragraph [0024], l.1-6 of the '397 application as published, wherein the DCs are defined as part of the DLC cell population. Said definition may be also found in the '480 patent application, on for instance p.3, l.4-12, . Therefore, Applicants assert that at least **claims 1 and 3, as amended** enjoy the benefit of the priority of the '480 application (**March 31, 1995**).

Previously presented Claims 5 to 10

In the description of the '480 application as originally filed, it is taught that DLC surface markers may be induced by treating the resting hybridomas with cytokines or other activating agents (for instance p.14, l.2-5). DLC characteristics include DC-morphology, DLC surface markers. DLC genetic markers and the capacity to activate immune cells in vitro (for instance p.13, l.22-23). Although said paragraphs refer to hybridomas; a skilled person who reads in the description that permanent cell lines may be developed from said plurality of hybrids (p.13, l.12-17), would conclude that this information also applies to the hybrids of the present invention. Consequently, previously presented **claims 5 to 8** may be granted the benefit of priority to the '480 application (**March 31, 1995**).

GM-CSF as an example of a cytokine is not taught in the '480 application. Therefore previously presented claims 9 and 10 may not be granted the benefit of priority to the '480 application.

Previously presented claims 11-14

That hybridomas may be irradiated or otherwise inactivated is taught, for example, on p.15, l.26 and p.16, l.4 of the '480 application as originally filed. It would have been clear for the

skilled person that this may also be applied when using a plurality of hybrids of the present invention. Consequently, the **previously presented claims 11 to 14** may be granted the benefit of priority to the '480 application (**March 31, 1995**).

Previously presented claims 15-18

Example 5 of the '480 application teaches that the hybridomas of the invention may be injected intra-peritoneal (p.27, l.26-27). Parenteral administration in an administration by means other than through the alimentary tract, which includes intra-peritoneal administration. Consequently, **new claims 15 to 18** may be granted the benefit of priority to the '480 application (**March 31, 1995**).

Claims 19, 20, 21, 22 and 47-50

Claims 19, 20, 21, 22, and 47-50 claim benefit of the priority of the '480 application. Indeed, support for said claims may be found on for instance p.12 l.16-20 and p.16, l.11 of the '480 application as originally filed.

Previously presented claims 23 and 24

The Examiner has granted the priority of the '502 application to claims 23 and 24 (**March 27, 1998**).

New claims 29 and 30

Support for new claims 29 and 30 may be found in for instance paragraph [0016], l.1-5 and [0019], l.2-4 (e.g. examples 7 and 8) of the '397 application as published. Said paragraphs correspond with p.6, l.11-14; p.6, l.23 to p.7, l.8 and p.30, l.9 to p.31, l.3 of the '480 application as originally filed. Therefore, the priority of the '480 application may be granted to new claims 29 and 30 (**March 31, 1995**).

New claims 31-46

Claims 31-46 refer to proliferating DCs or DCs at a more immature stage. Example 12 refers to the use of proliferating DC cells. As said example is not yet incorporated in the '480

application, the priority of said first application may not be granted for new claims 31-46. Example 12 was incorporated in the '502 application and the proliferating feature explained on p. 66, l.5-15 of said application. This aspect is also not taught in either of the '405 or '507 applications. Therefore, the priority date granted to new claims 31-46 is **March 27, 1998**.

As Guo et al (1994), Sornasse (1992) and US 5,637,483 are published (or filed) before March 31, 1995, they are valid as prior art to the present claims.

As claims 9, 10, 23-24 and 31-46 do not have the benefit the priority of the '480 application, the priority document US 5,851,756 needs to be considered for the subject-matter of claims 9, 10, 23-24 and 31-46.

Rejection under 35 U.S.C. § 103(a)

Claims 1, 3, and 19-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Guo, et al. (1994) in view of Sornasse, et al. (1992).

Non-obviousness of the subject-matter of claims 1 and 3

Claims 1 and 3 relate to a method of producing an anti-tumor response in a mammalian subject, said method comprising administering to said patient a plurality of dendritic/tumor cell hybrids or a dendritic cell/tumor hybridoma.

The Examiner explains that Guo et al. teach that hybrids (or hybridomas), comprising a bone marrow derived antigen-presenting B-cell and a tumor cell, induce a protective anti-tumor response upon administration to a subject. According to the Examiner, said teaching differs from the claimed invention only in that it does not teach the use of a DC as the antigen presenting component of the hybrid. Sornasse et al. teaches the superiority of DCs over B cells for in vivo use.

The Examiner further asserts that one skilled in the art would have been motivated based on both documents 1/ to produce a hybrid whereby the B-cell in the B-cell/tumor hybrid is

substituted by a DC cell as taught by Somasse et al, and, 2/ administer said product to a subject for the production of an anti-tumor response.

We respectfully disagree with the above ground of rejection. Applicants submit the Declaration of Dr. Moser along with the arguments below.

In a first instance we would like to point to the fact that by introducing a new definition into the claims for the term "dendritic cells", a clear distinction is made between the claimed subject-matter and the prior art.

Secondly, that the feasibility of making the DC/tumor hybrids is not predictable as discussed in the Declaration of Dr. Moser (section 2). In the Declaration, Dr. Moser indicates that it was not predictable at the time of the claimed invention that replacing the B cells of Guo, et al. with DC cells would provide the DC/tumor cell hybrids of the claimed invention because of observations at the time of the claimed invention that fusion of dissimilar cells often resulted in loss of expression of tissue specific traits. Thus, it was not predictable at the time of the claimed invention that DC /tumor cell hybrids (hybridomas) could be made which could be administered to produce an anti-tumor response as claimed. In addition, only based on the teaching of the present application (see examples 7-13 of the present application), may a skilled person predict that the production of said DC/tumor hybrids/hybridomas is feasible.

Third, Applicants assert that it is only based on the present invention and by using impermissible hindsight that a skilled person may expect that by producing said hybrid/hybridomas, cells may be created having characteristics of both DC and tumor cells which are needed to induce an anti-tumor response in a subject. This is also discussed in section 2a of the Declaration of Dr. Moser. As the Federal Circuit observed in Orthopedic Equipment Co. v. United States, 702 F.2d 1005, 217 U.S.P.Q. 193 (Fed. Cir. 1983):

> The question of nonobviousness is a simple one to ask, but difficult to answer...The difficulty which attaches to all honest attempts to answer this question can be attributed to the strong temptation to rely on hindsight while undertaking this evaluation. It is wrong to use the patent in suit as a guide through the references in the right way so as to

achieve the result of the claims in suit. Monday morning quarterbacking is quite improper when resolving the question of nonobviousness.

Fourth, the present invention proves for the first time that the hybrids/hybridomas of the present invention allow the efficient elimination of tumors in animals.

Finally, the approach followed by Guo et al. to produce said B-cell/tumor hybrids is not applicable to produce hybrids/hybridomas for in vivo treatment of animals, especially humans. This is extensively discussed in the Declaration of Dr. Moser (sections 2b and 3).

As is well-known, a prima facie case of obviousness requires that three basic criteria be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed invention and the reasonable expectation of success must both be found in the prior art, and must not be based on Applicants' disclosure. In the present case, the cited references, either alone or in combination, do not provide a reasonable expectation that the DC of Sornasse, et al. could be substituted for the B cells of Guo, et al. and that the resulting hybrids would produce an anti-tumor response upon administration to a subject.

Non-obviousness of the subject-matter of claims 19 to 24 and 47-50

The Examiner additionally noted that spleen cells of Guo and Sornasse et al would comprise an isolated DC as well as the only two murine subtypes of DC, i.e. myeloid and lymphoid, both of which derive from bone marrow.

Applicants are of the opinion that both the myeloid and lymphoid DC may be considered as isolated cells but are not different cell type to the latter. This is also confirmed in the Declaration of Dr. Moser (section 3).

Claims 19-20, 21-26, and 47-50 cover different subject-matter. New claims 19-20 and 47-50 focus on the part of the body (blood, bone marrow and lymph/lymph nodes) wherefrom the DC-fusion partners are sampled/purified; claims 21-24 relate to the cellular origin of the DC-fusion partners.

For this reason, claims 19 and 20 as amended focus on the *purification* of said cells and not on the *origin* of said cells. For the same reason new claims 47-50 have been formulated explaining alternative origins for the DC-fusion partner such as lymph /lymph nodes and blood. We refer to section 3 of the Declaration in respect of claims 21-24 and new claims 29-46.

Claims 19, 20 and 47-50 (the DC-fusion partner is preferably isolated from blood, bone marrow or lymph/lymph nodes)

It is true that (myeloid/lymphoid) DCs may be present in spleen. However, starting from spleen cells the feasibility of producing real DC/tumor cells is extremely low. This is illustrated in the present application (see examples 1-6 of the present application) and Guo et al. (1994). Both confirm that, when using spleen cells, mainly B-cell/tumor and T-cell/tumor hybrids can be formed. This is also argued in the Declaration of Dr. Moser (section 3).

The fact that DCs, derived from bone marrow, blood or other tissues are a better alternative to spleen cells (used by Guo and Sornasse) to start the production of the hybrids of the present invention was taught in the '397 application as originally filed and published (in for instance paragraph [0184]). The present invention teaches that said latter types of cells allow a more efficient production of DC/tumor hybrids/hybridomas.

We also refer in this respect to the fact that these bone marrow, lymph/lymph nodes and blood cells are easier to isolate and clinically more applicable. We also refer to section 3 of the Declaration of Dr. Moser,

As the subject matter of claims 19, 20 and 47-50 may not be derived from Guo et al. or by the combination of Guo et al. with Sornasse et al., we are of the opinion that claims 19-20 and 47-50, at least, are patentable under 35 U.S.C. § 103(a).

New claims 21-24 (the DC-fusion partner may be myeloid or lymphoid in origin)

We acknowledge that myeloid and lymphoid DCs originate from bone marrow DC precursors. This indeed covers general knowledge as pointed out by the Examiner.

However as pointed out by Dr. Moser (see section 3 of the Declaration) that the DC-fusion partner may be of myeloid or lymphoid origin represents a preferred embodiment of the invention that is neither taught nor suggested by the cited references.

In addition, as said claims 21-24 depend from claims 1 and 3 which are patentable for the reasons discussed above, claims 21-24 are also patentable.

In view of Applicants' amendments, arguments and the Declaration of Dr. Moser, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Claims 5-10 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Guo, et al.(1994) in view of Sornasse, et al. (1992) as applied to claims 1, 3, and 19-26 above and further in view of U.S. Patent No. 5,851,756.

Claims 5-10 relate to the method of the invention wherein the hybrids/hybridomas are further induced (preferentially by GM-CSF) before use, to express DC characteristics.

As discussed above, the effect of US 5,851,756 needs only to be considered for the novelty and non-obviousness of the subject-matter of claims 9 and 10.

The Examiner asserts that based on the '756 patent a skilled person would have been motivated to increase the number of said DCs (and thus DC characteristics) before use with GM-CSF.

Applicants do not agree that the '756 document compromises the non-obviousness of the subject-matter of claim 9 and 10 (or even claims 5-10). We refer in this respect to section 4 of the Declaration of Dr. Moser. In the Declaration, Dr. Moser points out that the DCs of the '756 patent are a different entity from the hybrids (hybridomas) taught by the present invention. Consequently, the '756 reference, either alone or in combination with the other cited references, provides no motivation to induce the hybrids/hybridomas as presently claimed.

Furthermore, since claims 5-10 depend ultimately from claims 1 and 3, which are neither taught nor suggested by the cited references, the invention defined in claim 5-10 is also patentably distinguished from the references, alone or in combination.

Applicants respectfully request the withdrawal of the rejection.

Claims 11-18 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Guo, et al. (1994) in view of Sornasse, et al. (1992) as applied to claims 1, 3, and 19-26 above, and further in view of U.S. Patent No. 5,637,483.

Claims 11-14

Claims 11-14 relate to the method of the invention wherein the hybrids/hybridomas are treated (preferentially using irradiation) to prevent proliferation. The Examiner asserts that the '483 patent teaches that a tumor cell-containing anti-tumor vaccine should be treated with irradiation to prevent proliferation. Therefore, the Examiner is of the opinion that one of ordinary skill in the art at the time of the invention would have been motivated to treat hybrids/hybridomas of the present invention to prevent proliferation as taught by the '483 patent.

Applicants do not agree that said documents compromise the non-obviousness of the subject-matter of claims 11-14 and refer to section 5 of the Declaration of Dr. Moser.

The teaching of claims 1, 3, and 11-14 of the present invention was not predictable based on Guo, Sornasse and the '756 patent. Consequently, the claims are patentable over the cited references. Furthermore, claims 11-14 depend from 1 and 3 and contain all of the limitations thereof. Claims 1 and 3 are patentable for the reasons presented above.

Reconsideration and withdrawal of this ground of rejection is respectfully requested.

Claims 15-18

The Examiner has rejected claim 15-18 as being unpatentable over Guo, et al. (1994) in view of Sornasse, et al. (1992) as applied to claims 1, 3, and 19-26 above, and further in view of U.S. Patent No. 5,637,483. The Examiner asserts that it would have been obvious to one of ordinary skill in the art to administer said hybrids/hybridomas by parenteral injection because this is the most well-known form of cell-based therapeutic administration. However, since claim 15-18 depend from claims 1 and 3, which are neither taught nor suggested by the cited references, the invention defined in claim 15-18 is also patentably distinguished from the references, alone or in combination. Applicants respectfully request the withdrawal of the rejection.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Nov. 10, 2003

By: Che S. Chereskin

Che Swyden Chereskin, Ph.D.
Registration No. 41,466
Agent of Record
Customer No. 20,995
(949) 760-0404

H:\DOCS\CSC\DECLE55\CP2DV\DECLE55CP2DV_AMD.DOC
110503